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U-shaped association between abnormal serum uric acid levels and COVID-19 severity: Reports from the Japan COVID-19 Task Force

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**Highlights:**

- We analyzed the serum uric acid levels and hyperuricemia in patients with COVID-19.
- High serum uric acid levels were associated with the requirement of IMV.
- Low serum uric acid levels were also associated with the requirement of IMV.

**Title:** U-shaped association between abnormal serum uric acid levels and COVID-19 severity:

Reports from the Japan COVID-19 Task Force

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**Abstract**

**Objectives:** This study aimed to identify the relationship between abnormal serum uric acid levels or a history of hyperuricemia and coronavirus disease 2019 (COVID-19) severity in the Japanese population.

**Methods:** We included 1,523 patients enrolled in the Japan COVID-19 Task Force cohort between February 2020 and May 2021. We compared the clinical characteristics, including comorbidities, laboratory findings, and outcomes, particularly invasive mechanical ventilation (IMV), among patients with and without abnormal uric acid levels or a history of hyperuricemia.

**Results:** Patients with high serum uric acid levels were older and had higher body weights and body mass index than those without. In addition, the multiple logistic regression analysis revealed a significant association between high serum uric acid levels or a history of hyperuricemia and an increased risk of IMV (odds ratio (OR)=1.77;  $p=0.03$ /OR=1.56;  $p=0.04$ ). Moreover, patients with low uric acid levels on admission were also associated significantly with the requirement of IMV (OR=5.09;  $p<0.0001$ ).

**Conclusion:** Abnormal serum uric acid levels or a history of hyperuricemia were significantly associated with COVID-19 severity in the Japanese cohort.

**Keywords**

COVID-19, hyperuricemia, hypouricemia, high serum uric acid, low serum uric acid, respiratory care, severity



## Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and is a worldwide pandemic. Until October 2021, there were more than 235 million confirmed COVID-19 cases and over 4.5 million confirmed deaths worldwide (Our World Data, 2021). The pandemic is still not displaying any signs of ending, making it difficult to deliver normal medical care. Limited medical resources warrant determining ways to provide appropriate treatment to individuals prone to this disease. Therefore, it is essential to understand the risk factors for severe COVID-19.

The risk factors for increasing COVID-19 severity include patient characteristics, such as men (Grasselli et al., 2020), obesity (Popkin et al., 2020), and age (O'Driscoll et al., 2021), in addition to comorbidities, such as hypertension (Pranata et al., 2020), chronic lung disease (Nishiga et al., 2020), and type 2 diabetes (Holman et al., 2020). Despite few reports on an association between a history of hyperuricemia and COVID-19 severity, a small retrospective study found that a history of hyperuricemia was associated with an increased COVID-19 mortality rate (Ishii et al., 2020).

Hyperuricemia increases the risk of hypertension (Fei et al., 2008) and cardiovascular disease (Cannon et al., 1966; Tuttle et al., 2001). The prevalence of hyperuricemia varies among countries (Wallace et al., 2004). In Japan, over 10 million patients present hyperuricemia. Approximately 30% of men in their 30s and 40s, and 25% of those in their 50s and 60s suffer from hyperuricemia; thus, it is a common condition that can also affect younger individuals (Japan Preventive Association of

Life-style related Disease, 2021). A history of hyperuricemia and abnormal serum uric acid levels are associated with several types of lifestyle-related diseases, and have been hypothesized to be associated with COVID-19 severity (Ghazanfari et al., 2021; Ishii et al., 2020; Zheng et al., 2021).

Previous reports have described an association between high serum uric acid levels and COVID-19 severity, particularly mortality or the rate of using invasive mechanical ventilation (IMV) (Ghazanfari et al., 2021; Zheng et al., 2021). However, researchers have also reported on an association between low serum uric acid levels and COVID-19 severity (Werion et al., 2020; Dufour et al., 2021). Some studies have shown a U-shaped association between serum uric acid levels and the risk of death (Cho SK, et al., 2018; Hu L, et al., 2020); hence, a similar association between serum uric acid levels and COVID-19 severity may exist. However, the precise relationship between COVID-19 severity and serum uric acid levels is unknown.

In this study, we aimed to identify the relationship between abnormal serum uric acid levels or a history of hyperuricemia and COVID-19 severity in a large Japanese cohort.

## Methods

### *Study design and Settings*

The study design and setting have been previously described (Tanaka et al., 2021).

All COVID-19 cases in this retrospective cohort study were recruited through the Japan COVID-19 Task Force. From February 2020 to May 2021, data were collected from consecutive inpatients aged  $\geq 18$  years and diagnosed with COVID-19, using the SARS-CoV-2 polymerase chain reaction

results at one of the affiliated hospitals (>100). The data of patients who agreed to participate in the study were registered in an electronic case record form. Patients meeting any of the following criteria were excluded: (i) non-Japanese; (ii) with incomplete medical records, such as the inability to obtain the use of invasive mechanical ventilation (IMV) or no data regarding the serum uric acid levels.

Among

the 1,976 patients who met the inclusion criteria, we excluded 51 non-Japanese patients. In addition, 379 patients with no data of serum uric acid levels and 23 patients with unknown IMV use were excluded. Thus, 1,523 patients were included in the analysis (Figure 1A).

Written or oral informed consent was obtained from all patients. This study was approved by the ethics committees of the Keio University School of Medicine (20200061) and related research institutions. All aspects of the study are conformed to the principles of the Declaration of Helsinki adopted by the WMA General Assembly, Fortaleza, Brazil on October 2013.

#### *Data collection and definitions*

We extracted the following information from the electronic case record forms: age, sex, body weight, body mass index (BMI), smoking history, clinical symptoms and signs, comorbidities, laboratory findings on admission, and disease severity (required IMV). All laboratory tests were performed according to the clinical care needs. The symptoms and signs were included during referral and admission in addition to during hospitalization. The laboratory results were collected

within 48 h of the initial visit or admission. Individual clinicians determined comorbidities, such as a history of

hyperuricemia and chronic kidney disease by conducting interviews with each patient or evaluating the electronic medical records. The recorded data were reviewed by a team of respiratory clinicians. For missing core data, the first clinician to diagnose the disease was contacted to collect it. Missing or absent data in the patient background were noted as unknown.

### *Statistical analysis*

Continuous and categorical variables are presented as means or percentages, respectively. The data were compared between the groups with and without a history of hyperuricemia using the *t*-test and  $\chi^2$  test, as appropriate. To investigate the relationship between serum uric acid levels or a history of hyperuricemia and IMV use, we performed a multivariable logistic regression analysis to adjust for previously analyzed factors (Hendren et al., 2021; Ishii et al., 2020;). The models were adjusted for age and chronic kidney disease (model 1), or additionally for sex, a history of hypertension, diabetes mellitus, chronic lung disease and cardiovascular disease (model 2). We presented the adjusted odds ratio (OR) with a 95% confidence interval (95% CI). Statistical significance was set at  $p < 0.05$ . All data were analyzed using the JMP 16 program (SAS Institute Japan Ltd., Tokyo, Japan).

## **Results**

*Comparison of baseline characteristics between patients with and without high serum uric acid levels on admission*

On the 1,523 patients included in this study, we performed an univariate logistic analysis to investigate the optimal cut-off value for the serum uric acid levels to predict the requirement of IMV. Receiver operating characteristic curves demonstrated that the optimal cut-off for baseline serum uric acid levels for predicting IMV requirement was 7.6 mg/dL (AUC 0.49;  $p=0.04$ ). The distribution of serum uric acid levels among the 1,523 patients is shown in Supplemental Figure 1. Hundred and thirteen patients had serum uric acid levels  $\geq 7.6$  mg/dL. Among them, 25 patients (22.1%) required IMV (Figure 1B). Table 1 summarizes the baseline characteristics of patients according to the baseline serum uric acid levels. Compared with patients with serum uric acid levels  $<7.6$  mg/dL, those with serum uric acid levels  $\geq 7.6$  mg/dL were more likely to be older ( $p=0.002$ ), and had a higher body weight ( $p=0.002$ ) and body mass index (BMI) ( $p=0.005$ ). There was no significant difference in the rate of each sign and symptom on admission, except for disturbance of consciousness ( $p<0.0001$ ) and sore throat ( $p=0.01$ ) between the groups. Hypertension, cardiovascular disease, and chronic kidney disease were observed in 58 (51.8%), 19 (16.8%), and 29 (26.4%) patients with serum uric acid levels  $\geq 7.6$  mg/dL, respectively, all with a statistically significant prevalence ( $p<0.05$ ). A history of hyperuricemia was also significantly more common in patients with serum uric acid levels  $\geq 7.6$  mg/dL ( $p=0.01$ ). The laboratory findings revealed higher white blood cells (WBC), c-reactive protein (CRP), and ferritin levels among patients with serum uric acid levels  $\geq 7.6$  mg/dL; with high blood urea nitrogen, creatinine, lactate dehydrogenase, potassium,

brain natriuretic peptide, HbA1c, and procalcitonin. Patients with serum uric acid levels  $\geq 7.6$  mg/dL also demonstrated a higher rate of bacterial infection than those without ( $p=0.003$ ).

#### *Association between serum uric acid levels and required IMV*

The rate of required IMV was significantly higher in patients with serum uric acid levels  $\geq 7.6$  mg/dL than in those with levels  $< 7.6$  mg/dL ( $p=0.0002$ ) (Figure 2A). Following an adjustment for the age and chronic kidney disease diagnosis in model 1, serum uric acid levels  $\geq 7.6$  mg/dL were independently associated with requirement of IMV in the multiple logistic regression analysis (odds ratio (OR)=1.77 [1.07–2.93];  $p=0.03$ ) (Figure 2B). The rate of death was also significantly higher in patients with serum uric acid levels  $\geq 7.6$  mg/dL ( $p<0.0001$ ) (Figure 3A). Patients with serum uric acid levels  $\geq 7.6$  mg/dL were also found an independent association with death (OR=2.72 [1.34–5.50];  $p=0.005$ ) (Figure 3B). The rate of oxygen required on admission was significantly higher in these patients ( $p=0.0002$ ) and was found to have a significant association on the multiple logistic regression analysis (OR=1.74 [1.08–2.78];  $p=0.02$ ) (Figure 4). In addition, among 969 patients who did not require oxygen on admission, those with serum uric acid levels  $\geq 7.6$  mg/dL was also associated with an increased risk of requiring IMV after admission ( $p=0.009$ ). However, among 284 patients who required oxygen on admission, high serum uric acid levels were not associated an increased risk of requiring IMV after admission ( $p=0.50$ ).

After adjustment for age, sex, history of chronic kidney disease, hypertension, diabetes mellitus, chronic lung disease and cardiovascular disease in model 2, serum uric acid levels  $\geq 7.6$  mg/dL were

associated with these following outcomes in the multiple logistic regression analysis (required IMV; OR=1.84 [1.09–3.09];  $p=0.02$ , death; OR=2.49 [1.19–5.19];  $p=0.02$ , required oxygen; OR=1.72 [1.06–2.80];  $p=0.03$ ). Using a serum uric acid cut-off value of  $>7.0$  mg/dL, which is the definition of hyperuricemia in Japan, the rate of required IMV was significantly increased ( $n=26$ ; 16.7%,  $p=0.03$ ). However, a serum uric acid level  $>7.0$  mg/dL was not significantly associated with IMV in the multivariable analysis (OR=1.28,  $p=0.32$ ).

Subsequently, we evaluated the association between the serum uric acid levels defined by various cut-off levels and the requirement of IMV using multivariable logistic regression analysis in model 1 (Figure 5). Patients with uric acid levels  $>8.5$  mg/dL, 8.0 mg/dL or 7.5 mg/dL were significantly associated with the requirement of IMV (OR=2.97 [1.59–5.56], 1.97 [1.14–3.42], and 1.77 [1.07–2.93]). In contrast, those with low uric acid levels  $<2.0$  mg/dL,  $<2.5$  mg/dL, or 3.0 mg/dL were also significantly associated with the requirement of IMV (OR=5.09 [2.43–10.64], 3.00 [1.69–5.32], 1.70 [1.06–2.70]). Likewise, after adjustment in model 2, these serum uric acid levels were associated with the requirement of IMV ( $<2.0$  mg/dL; OR=5.29 [2.36–11.85];  $p<0.0001$ ,  $<2.5$  mg/dL; OR=3.48 [1.87–6.47];  $p<0.0001$ ,  $<3.0$  mg/dL; OR=1.98 [1.20–3.28];  $p=0.008$ ,  $>8.0$  mg/dL; OR=1.99 [1.13–3.51];  $p=0.02$ ,  $>8.5$  mg/dL; OR=2.99 [1.57–5.71];  $p=0.0009$ ).

#### *Comparison of baseline characteristics between patients with and without a history of hyperuricemia*

Patients with a history of hyperuricemia were more likely to be men ( $p<0.0001$ ), older ( $p=0.001$ ) and had a higher body weight ( $p<0.0001$ ) and BMI ( $p<0.0001$ ) (Supplemental Table 1). Moreover,

they demonstrated significantly higher rates of hypertension ( $p<0.0001$ ), diabetes mellitus ( $p=0.0003$ ), cardiovascular disease ( $p<0.0001$ ) and chronic kidney disease ( $p<0.0001$ ). The laboratory findings demonstrated substantially higher ferritin ( $p<0.0001$ ), CRP ( $p=0.04$ ) in these patients.

The rate of required IMV was significantly higher in patients with a history of hyperuricemia than in those without ( $p=0.002$ ) (Supplemental Figure 2A). A history of hyperuricemia was independently associated with the requirement of IMV in the multiple logistic regression analysis following only model 1 (OR=1.56 [95% CI: 1.01–2.43];  $p=0.04$ ) (Supplemental Figure 2B).

## Discussion

This is the first study to report the relationship between uric acid levels and COVID-19 severity in a Japanese cohort. Furthermore, we first indicated that abnormal serum uric acid levels on admission and a history of hyperuricemia are associated with the requirement of IMV. Our findings could help us to predict the need for intubation and optimization of patient allocation for special therapies. Previous reports have described an association between low serum uric acid levels (Dufour et al., 2021; Liu et al., 2021; Li et al., 2021; Werion et al., 2020) and high uric acid (Ghazanfari et al., 2021; Zheng et al., 2021) and COVID-19 severity. In this study, high uric acid levels were associated with COVID-19 severity in terms of comorbidity; similarly, low uric acid levels were independently associated with COVID-19 severity. The Japanese definition of hyperuricemia (serum uric acid levels  $>7.0$  mg/dL) (Japan Preventive Association of Life-style related Disease, 2021) was not



significant; however, high uric acid level greater than the cutoff value of 7.6 mg/dL could predict the severity. In contrast, the Japanese definition of hypouricemia (serum uric acid levels  $<2.0\text{mg/dL}$ ) (Kuwabara et al., 2017) and low serum acid level greater than the cut-off value of  $2.5\text{mg/dL}$  could predict the severity. Both low and high uric acid levels were associated with COVID-19 severity outcomes, suggesting that the association between uric acid levels and COVID-19 severity may be mediated by more than one different pathogenic mechanism.

Uric acid is a product of purine metabolism and the serum uric acid level reflects the counterbalance between uric acid production and excretion. Serum uric acid level increases due to tissue damage. In the event of tissue damage, uric acid stored intracellularly is released from the cells, causing hyperuricemia (Ghazanfari et al., 2021; Zheng et al., 2021). Severe COVID-19 causes multiple pathophysiological effects, including oxidative stress, inflammation, endothelial dysfunction, renin-angiotensin-aldosterone system activation, and insulin resistance (Montiel et al., 2022, Govender et al., 2021, Vaduganathan et al., 2020). Our study revealed that the high inflammatory state may reflect tissue damage in patients with high serum uric acid levels on admission and it may progress to more severe outcomes after admission. This is supported by the result that patients with high serum uric acid levels already had a high rate of required oxygen upon admission. This inference could be made because of a Japanese cohort that was hospitalized based on background disease and other risk factors even in the absence of oxygen requirement. Therefore, high serum uric acid levels on admission may serve to act as a direct biomarker of COVID-19 severity.

Meanwhile, patients with high uric acid levels on admission demonstrated several baseline characteristics that have been previously associated with COVID-19 severity. First, these patients were older (O'Driscoll et al., 2021), smokers (Shastri et al., 2021; World Health Organization, 2021), and obese (Zheng et al., 2020). Second, their comorbidities included hypertension (Bailly et al., 2021), diabetes mellitus (Ando et al., 2021; Fried et al., 2021), cardiovascular disease (Nishiga et al., 2020), and chronic kidney disease (Cheng et al., 2020; Genovesi et al., 2021; Petrilli et al., 2020; Sullivan et al., 2021; Williamson et al., 2020). In addition, poor prognostic laboratory biomarkers were higher in these patients (D-dimer (Xu et al., 2020), CRP (Brasen et al., 2021), and ferritin (Deng et al., 2021)). These may reflect a complex interaction of uric acid levels and COVID-19 severity. The aforementioned comorbidities may be confounding factors in the association between the history of hyperuricemia and the requirement for IMV in patients with COVID-19. However, abnormal serum uric acid levels were independently associated with IMV after adjusting for these risk factors. Likewise, patients with a history of hyperuricemia also demonstrated similar baseline characteristics and this was found to be independently associated with the requirement of IMV after adjusting for age and chronic kidney disease. However, the history of hyperuricemia was not an independent factor in model 2, which included multiple comorbidities, presumably due to the confounding effect with other comorbidities or the effect of the lowering of the uric acid levels by a hyperuricemia drug. Therefore, from our study, patients with high uric acid levels on admission or a history of hyperuricemia can be assumed to have an independent factor predicting COVID-19 severity. We previously reported on the relationship between hyperuricemia-related genes and

COVID-19 severity in a large genome-wide association study (Namkoong et al., 2021). Thus, genetic predisposition to hyperuricemia is also supposedly related to COVID19 severity, which supports the results of our study.

Interestingly, our findings demonstrated that low serum uric acid levels on admission also associated significantly with IMV requirement. The AUC of the receiver operating curve for baseline serum uric acid levels was relatively low. This was because not only high serum uric acid levels, but also low serum uric acid levels, were associated with IMV use. Low serum uric acid levels may more directly reflect COVID-19 severity via renal tubular dysfunction. Previously, a clinical and autopsy study reported evidence for proximal tubule dysfunction in a subset of patients with COVID-19, with low-molecular-weight proteinuria, neutral aminoaciduria, and defective handling of uric acid or phosphate (Werion et al., 2020; Dufour et al., 2021). The above-mentioned studies confirmed the relationship between low serum uric acid levels and COVID-19 severity, such as the rate of IMV use and death. Serum uric acid levels are lowest 2–3 weeks post-hospitalization and subsequently increase (Liu et al., 2021); thus, low serum uric acid levels are also a possible biomarker reflecting COVID-19 severity via renal dysfunction, particularly proximal tubule dysfunction.

This study had some limitations. First, we extracted the history of hyperuricemia and chronic kidney disease by conducting interviews with each patient or evaluating the medical records. The criteria for extraction of the history of hyperuricemia or chronic kidney disease may have differed among individual institutions. Only 10% of patients had a history of hyperuricemia in this study, which is less than the prevalence of hyperuricemia in the Japanese population (20–30%) (Japan

Preventive Association of Life-style related Disease, 2021). It may have resulted in a lower prevalence than the actual prevalence. The same is assumed regarding the history of chronic kidney disease. Thus, undiagnosed chronic kidney disease could be a confounding factor in the association between a history of hyperuricemia and COVID-19 severity. In addition, we did not record regular patient medications, and it was impossible to determine whether hyperuricemia was being currently treated, treated previously, or only recorded. We speculate that in patients with abnormal serum uric acid levels, the regular use of hypouricemia drugs may be effective in preventing the severity of COVID-19. This warrants further studies evaluating the effectiveness of hyperuricemia treatment for COVID-19. Second, the duration between the disease onset and the collection of serum uric acid levels was unclear. Blood samples were collected during hospitalization within 48 h. Moreover, the serum uric acid levels vary among patients with COVID-19. One study reported that low serum uric acid levels last for only 4 days and subsequently increase (Dufour et al., 2021), contrary to others. We did not examine the changes in serum uric acid levels following hospitalization, which made the interpretation difficult. This necessitates further studies to address the aforementioned limitations in the future.

## **Conclusion**

In a large Japanese cohort study, we evaluated the correlation between abnormal serum uric acid levels or a history of hyperuricemia and COVID-19 severity. Our findings indicated an association between abnormal serum uric acid levels or a history of hyperuricemia and COVID-19

severity, such as IMV use, suggesting a prognostic role in patients with COVID-19. More studies are required to evaluate the complex associations between abnormal serum uric acid and COVID-19 severity.

### **Declaration of competing interest**

The authors declare that they have no conflicts of interest.

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### **Ethics approval**

This study was approved by the ethics committee of the Keio University School of Medicine (20200061) and affiliated institutes.

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contributed to this study. Supplemental files named “Author information” summarizes the members who contributed to the collection and analysis of cases at each institution.

### **Author’s contribution**

Conceptualization: T.F., S.C., H.N., K.M., H.K., M.I., N.H., and K.F. Data curation: T.F., K.N., H.T., H.L., A.M., S.O., M.W., and T.K. Formal analysis: T.F., S.C. Methodology: T.F., S.C., and H.N. Supervision: S.C., N.H., K.M., H.K., M.I., N.H., N.H., T.U., S.U., T.I., K.A., F.S., T.Y., Y.N., Y.M., Y.S., K.M., Y.O., R.K., Y.K., A.K., S.I., S.M., S.O., T.K., and K.F. Visualization: S.C., H.N. Writing—original draft: T.F., S.C. Writing—review and editing: T.F., S.C., N.H., K.M., H.K., M.I., N.H., N.H., T.U., S.U., T.I., K.A., F.S., T.Y., Y.N., Y.M., Y.S., K.M., Y.O., R.K., Y.K., A.K., S.I., S.M., S.O., T.K., and K.F.

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**Appendix. Supplementary materials**

The following are supplementary data to this article.

**Supplementary Figure captions**

Supplemental Figure 1. The proportion of serum uric acid levels among the 1,523 patients

Supplemental Figure 2. The relationship between patients with COVID-19 and a history of hyperuricemia and their outcomes

A. The proportion of using invasive mechanical ventilation (IMV) between patients with and without a history of hyperuricemia.

B. Multivariable logistic regression analysis for the relationship between patients with COVID-19 and a history of hyperuricemia and their outcomes.

**Figure captions**

Figure 1. Consort diagram of patient selection

A. Overall 1,976 patients with COVID-19 have been registered during the study period, and 1,523 patients were included in the analysis.

B. The study included 1,523 patients, and was stratified by optimal cutoff for baseline serum uric acid levels ( $<7.6$  mg/dL or  $\geq 7.6$  mg/dL)

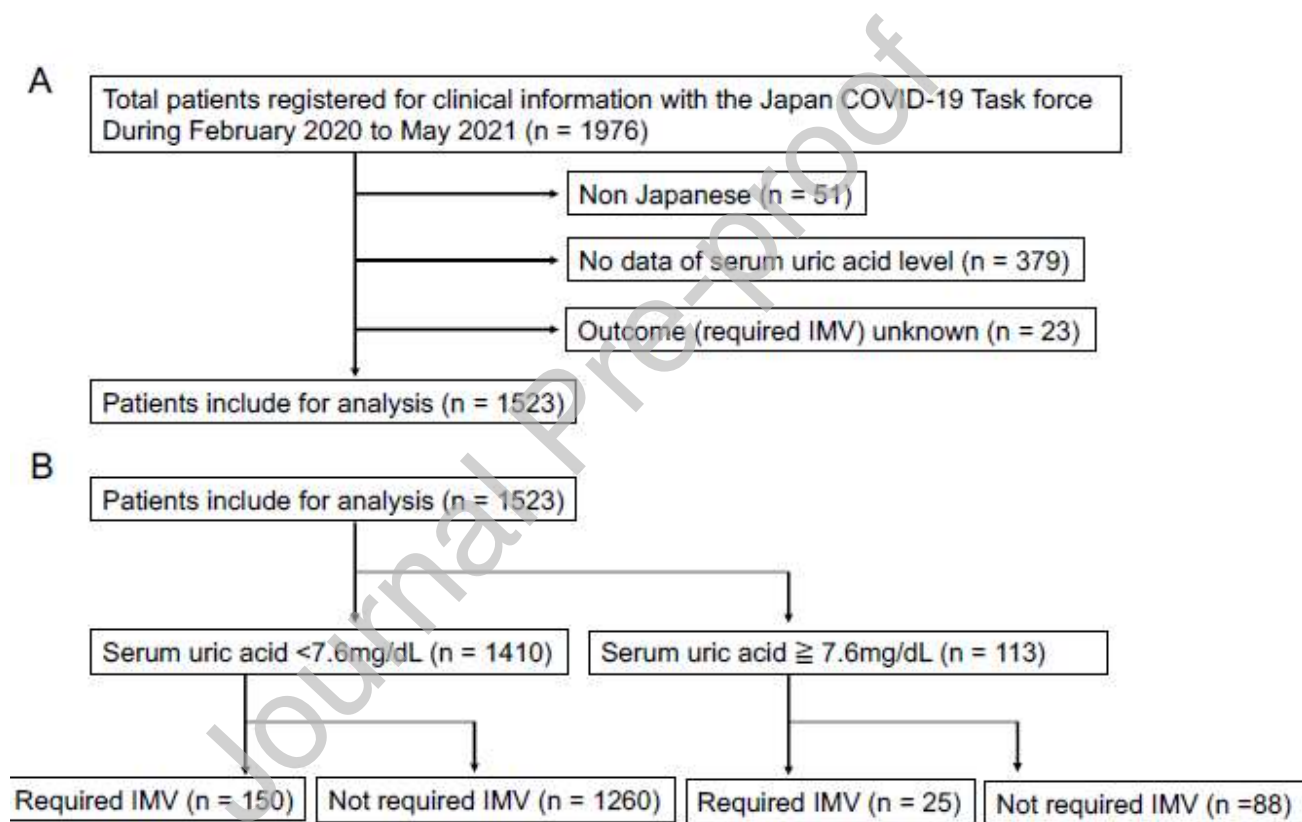




Figure 2. The relationship between patients with COVID-19 and high serum uric acid levels on admission and their outcomes (required invasive mechanical ventilation (IMV))

A. The proportion of requirement of IMV in patients with and without high serum uric acid levels on admission.

B. Multivariable logistic regression analysis for the relationship between patients with COVID-19 and high serum uric acid levels on admission and required IMV.

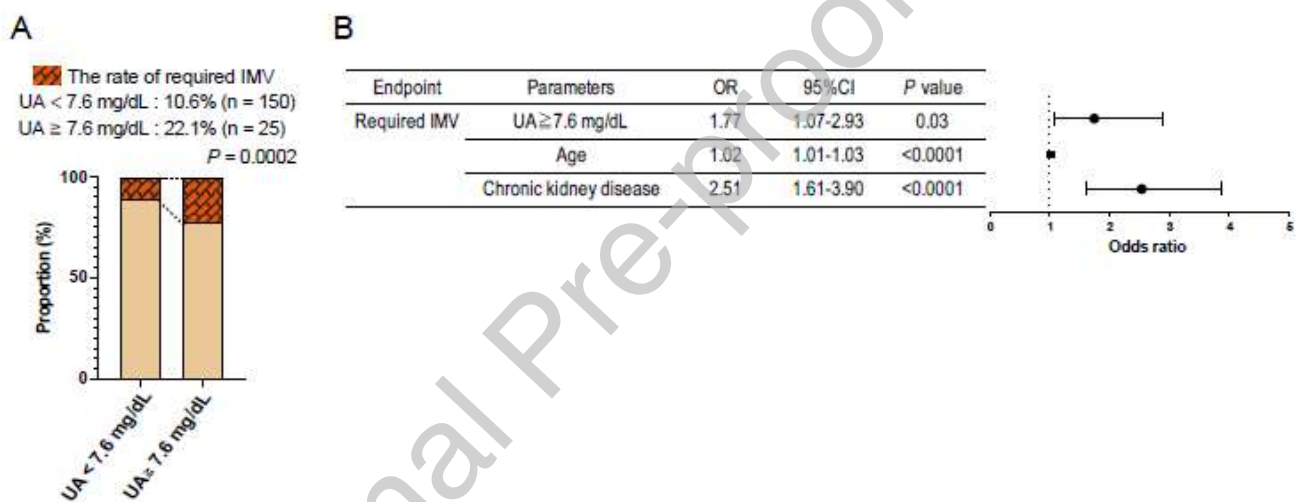


Figure 3. The relationship between patients with COVID-19 and high serum uric acid levels on admission and their outcomes (death)

A. The proportion of death in patients with and without high serum uric acid levels on admission.

B. Multivariable logistic regression analysis for the relationship between patients with COVID-19 and high serum uric acid levels on admission and death.

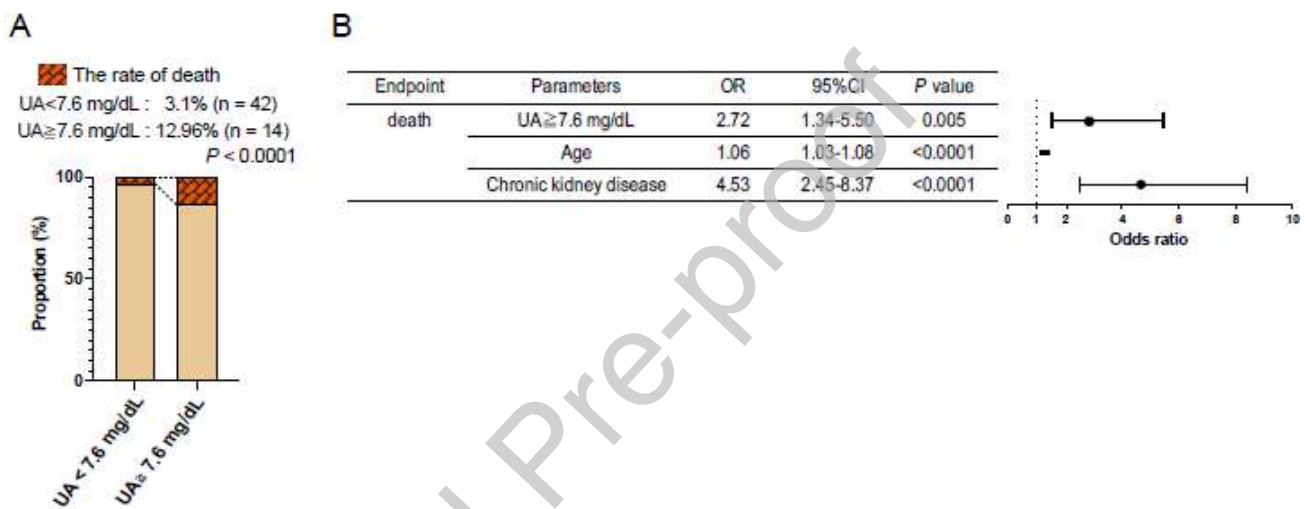


Figure 4. The relationship between patients with COVID-19 and high serum uric acid levels on admission and required oxygen

A. The proportion of required oxygen in patients with and without high serum uric acid levels on admission.

B. Multivariable logistic regression analysis for the relationship between patients with COVID-19 and high serum uric acid levels on admission and requirement of oxygen.

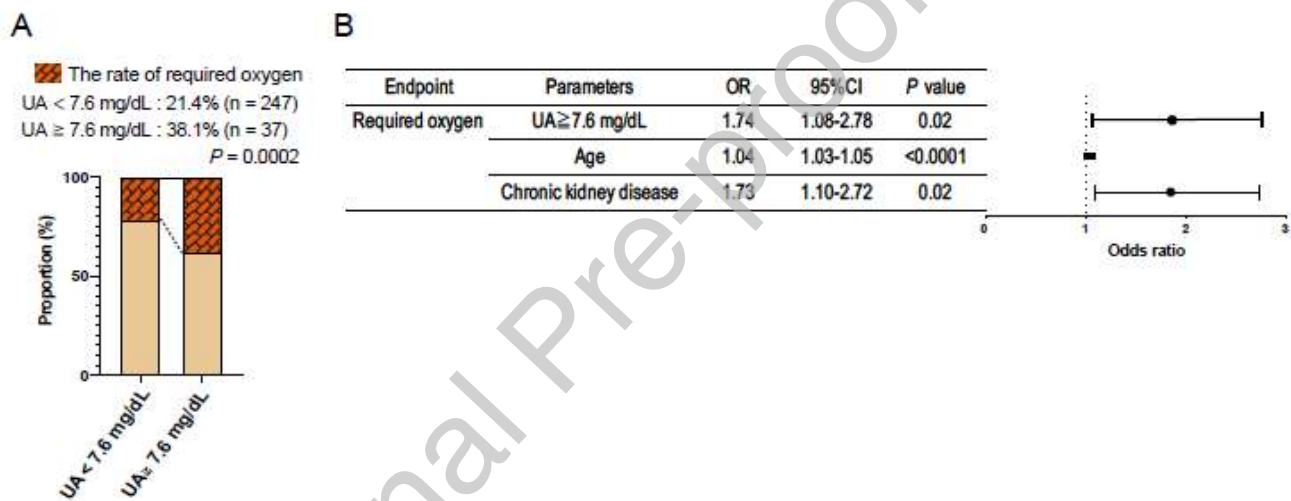


Figure 5. Multivariable logistic regression analysis for IMV use by serum uric acid levels

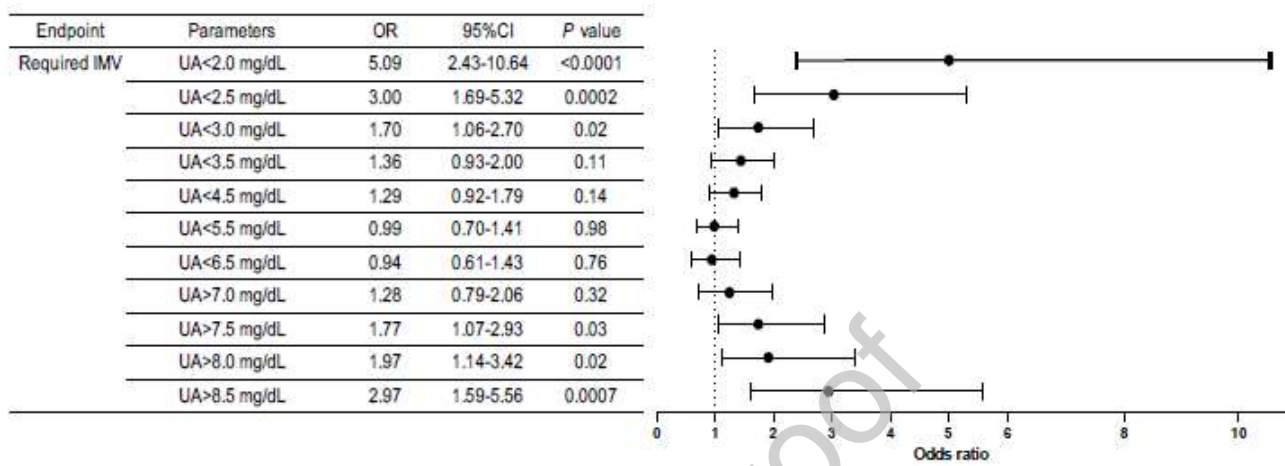


Table 1.

A comparison of the characteristics between the patients with uric acid levels  $<7.6$  mg/dL and  $\geq 7.6$  mg/dL on admission

Parameters	All patients n=1523	UA $<7.6$ mg/dL n=1,410	UA $\geq 7.6$ mg/dL n=113	p-value
Age, mean (95% CI)	59.3 (58.4-60.1)	58.9 (57.9-59.8)	63.9 (60.7-67.2)	0.002
Sex, n (%)				
Male	1023 (67.2)	939 (66.6)	84 (74.34)	
Female	500 (32.8)	471 (33.4)	29 (25.7)	0.09
Body weight, median (95%CI)	67.0 (66.1-67.8)	66.6 (65.7-67.5)	71.8 (68.6-75.0)	0.002
BMI, median (95%CI)	24.6 (24.4-24.9)	24.5 (24.2-24.8)	25.9 (25.0-26.9)	0.005
Smoking history				
Current smoker, n (%)	222 (15.3)	199 (14.8)	23 (21.7)	0.08
Ex smoker, n (%)	666 (46.3)	609 (45.8)	57 (53.3)	0.19
Brinkman index, median (95%CI)	671.6 (602.2-741.0)	676.9 (604.2-749.6)	616.1 (380.1-852.0)	0.77
Signs and symptoms, n (%)				
Disturbance of consciousness	56 (3.7)	44 (3.2)	12 (10.7)	$<0.0001$
Fever	1182 (78.3)	1095 (78.4)	87 (77.7)	0.85
Cough	862 (57.4)	805 (57.8)	57 (51.8)	0.22
Sputum	356 (23.7)	328 (23.6)	28 (25.2)	0.7
Sore throat	346 (23.1)	331 (24.0)	15 (13.3)	0.01
Nasal discharge	227 (15.2)	216 (15.6)	11 (9.8)	0.1
Dysgeusia	267 (17.8)	254 (18.3)	13 (11.5)	0.07

Dysosmia	245 (16.4)	232 (16.8)	13 (11.5)	0.23
Dyspnea	475 (32.1)	432 (31.6)	43 (39.1)	0.1
Malaise	736 (49.0)	676 (48.7)	60 (53.1)	0.37
Comorbidities, n (%)				
Hyperuricemia	177 (11.8)	156 (11.2)	21 (19.1)	0.01
Hypertension	560 (37.3)	502 (36.2)	58 (51.8)	0.001
Diabetes mellitus	355 (23.5)	321 (22.9)	34 (30.6)	0.07
Cardiovascular disease	164 (10.8)	145 (10.4)	19 (16.8)	0.03
Chronic lung disease	76 (5.1)	66 (4.7)	10 (9.1)	0.04
Chronic kidney disease	130 (9.0)	101 (7.6)	29 (26.4)	<0.0001
Laboratory findings, median (95% CI)				
WBC ( $\times 10^3$ /dL)	5.8 (5.7-6.0)	5.8 (5.6-6.0)	6.5 (5.9-7.0)	0.02
Neutrocyte (fraction, %)	69.9 (69.2-70.6)	69.8 (69.1-70.5)	71.2 (68.8-73.8)	0.27
Lymphocyte (fraction, %)	21.6 (21.0-22.3)	21.8 (21.2-22.5)	19.2 (16.8-21.5)	0.03
Eosinocyte (fraction, %)	0.87 (0.77-0.98)	0.87 (0.76-0.98)	0.89 (0.51-1.28)	0.91
Hemoglobin (g/dL)	14.0 (13.9-14.1)	14.0 (13.9-14.1)	13.6 (13.3-14.0)	0.04
Platelet ( $\times 10^4$ /dL)	19.8 (19.4-20.1)	19.9 (19.5-20.3)	18.5 (17.2-19.8)	0.05
Albumin (g/dL)	3.7 (3.6-3.7)	3.7 (3.7-3.8)	3.5 (3.4-3.6)	0.0003
T-Bil (mg/dL)	0.68 (0.66-0.70)	0.68 (0.66-0.70)	0.63 (0.56-0.71)	0.23
$\gamma$ GTP (U/L)	66.5 (62.0-70.9)	66.3 (61.7-71.9)	68.5 (52.1-85.0)	0.8
AST(U/L)	42.0 (38.4-45.7)	40.9 (37.1-44.7)	56.3 (43.0-69.6)	0.03
ALT(U/L)	40.0 (35.1-44.7)	39.4(34.4-44.3)	46.5 (29.1-64.0)	0.44

BUN (mg/dL)	17.8 (17.1-18.6)	16.6 (15.9-17.4)	32.4 (29.8-35.1)	<0.0001
Creatinine (mg/dL)	1.15 (1.07-1.23)	1.04 (0.96-1.13)	2.5 (2.23-2.82)	<0.0001
LDH (U/L)	276 (270-283)	272 (265-278)	330 (307-354)	<0.0001
Uric acid (mg/dL)	4.9 (4.8-5.0)	4.6 (4.5-4.6)	9.2 (8.9-9.4)	<0.0001
CK (U/L)	158 (134-183)	150 (124-175)	257 (167-346)	0.02
Na (mEq/L)	138.3 (138.1-138.5)	138.3 (138.1-138.5)	138.3 (137.6-139.0)	0.95
K (mEq/L)	3.99 (3.97-4.02)	3.98 (3.96-4.00)	4.14 (4.05-4.23)	0.0003
Cl* (mEq/L)	101.9 (101.7-102.1)	101.9 (101.7-102.1)	101.6 (100.9-102.4)	0.51
BNP (pg/mL)	73.0 (45.9-100.0)	62.8 (34.9-90.8)	206.8 (105.1-308.4)	0.008
Ferritin (ng/mL)	560 (526-594)	549 (514-584)	703 (573-833)	0.03
HbA1c (%)	6.4 (6.3-6.5)	6.4 (6.3-6.4)	6.7 (6.4-6.9)	0.04
D-dimer (ng/mL)	2.5 (2.0-2.9)	2.2 (1.8-2.7)	5.2 (3.7-6.7)	0.0002
Procalcitonin (ng/mL)	0.28 (0.20-0.35)	0.25 (0.17-0.32)	0.68 (0.41-0.94)	0.003
CRP (mg/dL)	4.9 (4.6-5.2)	4.8 (4.5-5.1)	5.9 (4.9-7.0)	0.04
Complication of bacterial infection, n (%)	187 (12.4)	163 (11.6)	24 (21.2)	0.003
Required oxygen therapy, n (%)	284 (22.7)	247 (21.4)	37 (38.1)	0.0002

Abbreviations; AST=aspartate transaminase, ALT=alanine transaminase, BMI=body mass index,  
 BNP=brain natriuretic peptide, BUN=blood urea nitrogen, CK=creatinine kinase, CI=confidence interval,  
 Cl\*=chloride, CRP=C-reactive protein, K=kalium, LDH=lactate dehydrogenase,  
 Na=sodium,  
 and WBC=white blood cell.

The *p*-values compared the data between the patients with and without hyperuricemia during hospitalization

using the Pearson's chi-square test.

#### **Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: